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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,522	04/12/2006	Nafizal Hossain	06275-503US1	3659

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
03/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,522	HOSSAIN, NAFIZAL	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 6-10, 12-42* is/are pending in the application.

4a) Of the above claim(s) *8,10 and 12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,9 and 19-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 6-10, 12-42 are pending in the current application. Claims 1-2, 6-7, 9, 19-42 are under examination. Claims 8, 10, 12-18 are withdrawn from consideration.

2. This is a National Stage of PCT/SE2004/001476, filed October 14, 2004, which claims priority to Swedish Application Serial No. 0302755-4, filed October 17, 2003.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The rejection of claims 1-2, 6, 9, and new claims 19-38 under 35 U.S.C. 112 1st paragraph for scope of enablement is maintained. The examiner served to show the scope that is enabled by the specification, in terms of the compounds, and the teaching of the prior art. The very limited disclosure and the inordinate amount of experimentation required to practice the invention, clearly warrant the conclusion made by the examiner, which was supported by references testifying to the state of the art and its unpredictability. Applicant's representative has continued to argue substantially the same line of reasoning as previously argued and such duplicate arguments will not be addressed here.

The presentation of the genus in the remarks of November 24, 2008 on page 19 is misleading. In the first instance the description given fails to include the complete definition of the variable R_3, which represents two of the three pages of variable definitions. The genus can be easily examined by looking at instant claim 1, which was not reproduced in its entirety on page 19. The five working examples show only R^1 as chlorine and R^9 as either fluorine or OH. R^8 is exemplified only as H or methyl. For R^3 the only moiety exemplified is –NHC=OMe or –

C=ONHMe. The examiner's position is that these examples do not support the genus as claimed. The applicant's representative has a different view of the state of the art and the level of experimentation required to practice the claimed invention. The examiner submits that a skilled artisan, Derek Lowe, a Ph.D. medicinal chemist who has worked for numerous drug companies and runs the website "In the Pipeline" describes disclosures like that of the instant case in the following way:

"I've seen many claims that couldn't be fully enabled short of putting five hundred people to work on them full-time for about ten years." (In the Pipeline, online, accessed June 16, 2008, "http://pipeline.corante.com/archives/2006/01/24/the_examiner_finally_snaps.php")

Actually it is not physically possible to synthesize the full scope of the instant claims no matter how much time or manpower that was at one's disposal, because they are indefinitely extensible. For example the group R^{10} which is part of one of the definitions of R^3 is defined in the following manner:

> R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and $-NHC(O)-R^{13}$
>
> R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;
>
> R^{13} represents a C_1-C_6 alkyl, amino or phenyl group;
>
> R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, C_1-C_6 alkylsulphonyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

If R^{10} is a group $NR^{14}R^{15}$ and each $R^{14}R^{15}$ represents phenyl and each phenyl is optionally substituted by one of the substituents as defined for R^{10}, such a substituent group selected from $NR^{14}R^{15}$ and each $R^{14}R^{15}$ represents phenyl and each phenyl is optionally substituted by one of the substituents as defined for R^{10}, such a substituent group selected from $NR^{14}R^{15}$ and each $R^{14}R^{15}$ represents phenyl and each phenyl is optionally substituted by one of the substituents as defined for R^{10} .....and so on to no end. So contra to the applicant's assertion that the genus of claim 1 is "a narrow, well defined genus of compounds." it is clear that it actually has no end.

The applicant's representative has also argued that the evidence proffered in the rejection under the "how to use" requirement the articles by both Ting, Thoma, Brown and Xie, were drawn to compounds of a different structure. These references are in the very same field of chemokine receptor antagonists and clearly show the unpredicitable nature of developing small molecule ligands at these receptors. The compounds disclosed in the instant case would need to overturn all knowledge about the unpredictability in the development of chemokine receptor ligands and posses a pharmacophore immune to perturbation by groups as large as infinity. The theurgical pharmacophore required to support such a genus is not supported by the statements of

the specification regarding biological activity. The applicant's representative has submitted data for the five example compounds, however this should be submitted in an affidavit signed by the inventors. Regardless, submission of data for five compounds does not support the scope claimed for the reasons of record.

The examiner would like to suggest that should the instant claims be amended to limit the definition of R^1 to halogen, R^9 as either halogen or OH, and R^{10}, R^{11}, and R^{12} as H or alkyl. This we be an appropriate representation of the genus, i.e. the R^1 example of chlorine would represent the genus halogen, the R^9 example of fluorine represent the genus halogen, and the R^{10}, R^{11}, and R^{12} example of methyl would support a claim to alkyl, or in the alternative variable definitions as defined in the new claims 39-42.

The double patenting rejections are maintained for the reasons of record. The applicant's representative has attempted to characterize the examiner's statement, that "One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties." as using the instant disclosure in the rejection, as evidenced by the following statement "However, the claimed compounds and their properties are only taught in the present specification, and not in the prior art of record. The Office cannot rely on equivalence known only to Applicants". The examiner does not understand the nature of this argument, because as is well established that expected results are evidence of obviousness, see In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." (resultant decrease of dental enamel solubility accomplished by adding an acidic

buffering agent to a fluoride containing dentifrice was expected based on the teaching of the prior art); Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims at issue were directed to a process of sterilizing a polyolefinic composition which contains an antioxidant with high-energy radiation. Although evidence was presented in appellant's specification showing that particular antioxidants are effective, the Board concluded that these beneficial results would have been expected because one of the references taught a claimed antioxidant is very efficient and provides better results compared with other prior art antioxidants.).

This consideration of unexpected results is separate from that of in Re Dillon as quoted in the remarks where, "To rely on an equivalence known only to the applicant to establish obviousness is to assume that his disclosure is a part of the prior art. The mere statement of this proposition reveals its fallaciousness." The examiner has used the U.S. Pre-Grant Publication 2006/0252751 as evidence of the equivalence, not the specification. Only a one-way determination of obviousness is needed in resolving the issue of double patenting.

A new ground of rejection under 112 2nd paragraph has been raised for the failure of claim 1 to delineate the identity of a claim element (i.e. R2). Claim 29 is rejected for the "preferably" language.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, R2 has no definition.

5. Claim 29-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 29, the language "preferably" is used. It is improper to speak of preferred embodiments within a claim. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

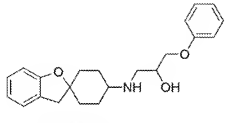
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-2, 6-7, 9, 19-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10 of copending Application No. 10/579,545 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

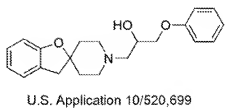
Determination of the scope and content of the prior art

(MPEP 2141.01)

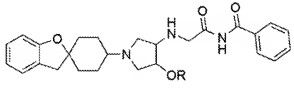
Xue et. al. teaches spiro[benzofuran-2,1'-cyclohexan]-4'-amines that are chemokine antagonists. 10/579,545 teach spiro[benzofuran-2,4'-piperidines bearing a 1-phenoxy-3-propan-2-ol substituent on the piperidinyl nitrogen atom. This relationship is illustrated graphically in Figure 1.



Instant case



U.S. Application 10/520,699

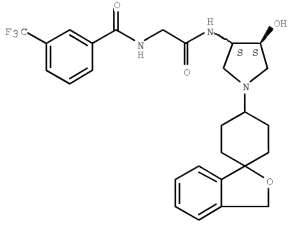


Xue et. al.

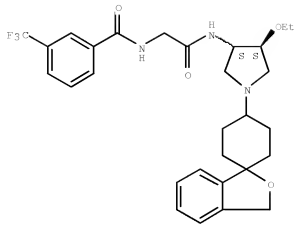
Figure 1. Structures of compounds that form the basis of the obviousness rejection as compared to the instant invention.

Some of the compounds disclosed by Xue are show below:

Registry #: 709018-09-7



Registry #: 709019-00-1



Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene group. By inserting a what is formally a methylene (CH_2 actually CH in the ring and H on N) into the compounds of Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite a spiro[benzofuran-2,1'-cyclohexan]-4'-amine is produced, which is a core pharmacophore of chemokine antagonism. These relationships are illustrated graphically in Figure 2.

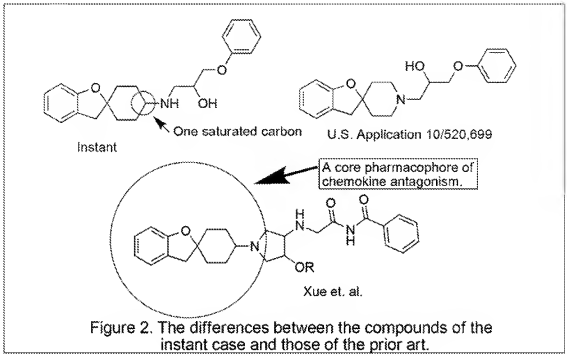


Figure 2. The differences between the compounds of the instant case and those of the prior art.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-2, 6-7, 9, 19-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12 of copending Application No. 10/581,171 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. This is a provisional obviousness-type double patenting rejection.

7. Claims 1-2, 6-7, 9, 19-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, 14 of copending Application No. 10/583,468 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. Although claim 9 is apparently a claim for "a claim".

8. Claims 1-2, 6-7, 9, 19-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13 of copending

Application No. 10/520,699 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 5-6, 9, 19-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

> *(A) The breadth of the claims;*
> *(B) The nature of the invention;*
> *(C) The state of the prior art;*
> *(D) The level of one of ordinary skill;*
> *(E) The level of predictability in the art;*
> *(F) The amount of direction provided by the inventor;*
> *(G) The existence of working examples; and*
> (H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions (B) The nature of the invention: This is a chemical

invention requiring the synthesis of compounds. (D) The level of one of ordinary skill: One of ordinary skill is a practicing organic chemist. (C) The state of the prior art: Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. (E) The level of predictability in the art: Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)……." Dorwald

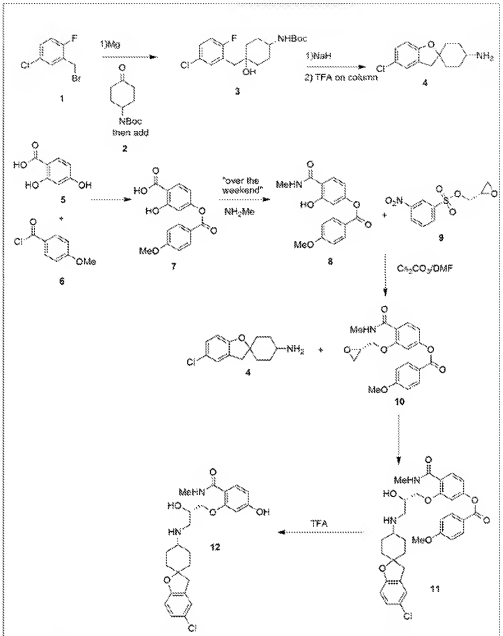
F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

As per MPEP:

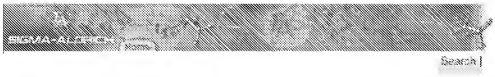
> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

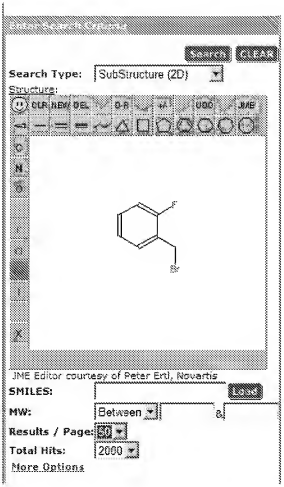
The synthetic route and starting materials that the applicant has provided to make the scope of this invention has been reproduced below as Scheme1:



Scheme 1. The chemistry relied on to construct applicant's compounds.

The key materials here are the α-bromo-2-fluoro-toluene derivative 1, the N-Boc-4-amino cylcohexanone 2, phenols such as 8 bearing amide groups, and glycidols 9. A search for each of these materials in the Aldrich Chemical Company catalog (St. Louis, MO) was conducted, the results of which are reproduced below:


SIGMA-ALDRICH
Home
Search


Search
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SubStructure (2D)
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SMILES:
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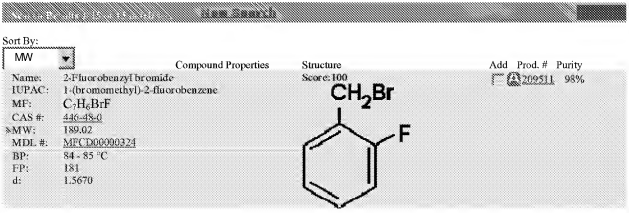
Between
Results / Page:
50
Total Hits:
2000
More Options


New Search
Sort By:
MW
Compound Properties
Structure
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Prod. #
Purity
Name: 2-Fluorobenzyl bromide
Score: 100
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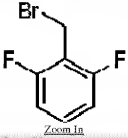
98%
IUPAC: 1-(bromomethyl)-2-fluorobenzene
MF: C7H6BrF
CAS #: 446-48-0
MW: 189.02
MDL #: MFCD00000324
BP: 84 - 85 °C
FP: 181
d: 1.5670
CH2Br
F

Zoom In

Name: 2,6-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 85118-00-9
MW: 207.02
MDL #: MFCD00000329
FP: 230

Score:96

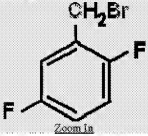


Zoom In

83141 purum, ≥95.0% (GC)
264431 97%

Name: 2,5-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,4-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 85117-99-3
MW: 207.02
MDL #: MFCD00009897
FP: 60
d: 1.6090

Score:84

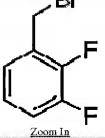


Zoom In

264423 98%

Name: 2,3-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 113211-94-2
MW: 207.02
MDL #: MFCD00042488
FP: 194
d: 1.6280

Score:86

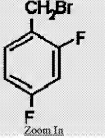


Zoom In

68318 ≥99.5% (GC)
74259 purum, ≥99.5% (GC)
265314 98%

Name: 2,4-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,4-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 23915-07-3
MW: 207.02
MDL #: MFCD00011649
FP: 104
d: 1.6130

Score:90



Zoom In

264415 98%

Name: 2-Chloro-6-fluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1-chloro-3-fluorobenzene
MF: C_7H_5BrClF
CAS #: 68220-26-8
MW: 223.47
MDL #: MFCD00040126
FP: 230
d: 1.6290

Score:69

Zoom In

539090 96%

Name: 2,3,6-Trifluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,3,4-trifluorobenzene
MF: $C_7H_4BrF_3$
CAS #: 151412-02-1

Score:84

449407 97%

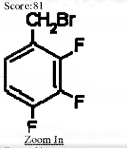
MW: 225.01
MDL #: MFCD00061208
BP: 114 °C
FP: 195
d: 1.7180

Zoom In

Name: 2,3,4-Trifluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3,4-trifluorobenzene
MF: $C_7H_4BrF_3$
CAS #: 157911-55-2
MW: 225.01
MDL #: MFCD00061233
FP: 195
d: 1.71

Score:81

554685 97%

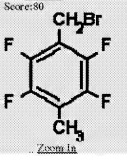


Zoom In

Name: 1-Bromomethyl-4-methyl-2,3,5,6-tetrafluorobenzene
IUPAC: 1-(bromomethyl)-1,2,3,5,6-tetrafluoro-4-methylbenzene
MF: $C_8H_5BrF_4$
CAS #: 92814-00-1
MW: 257.02
MDL #: MFCD03091156
FP: 199

Score:80

556491 97%

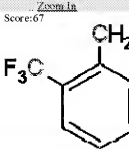


Zoom In

Name: 2-Fluoro-6-(trifluoromethyl)benzyl bromide
IUPAC: 2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene
MF: $C_8H_5BrF_4$
CAS #: 239087-08-2
MW: 257.02
MDL #: MFCD00082477
FP: 225

Score:67

539627 98%

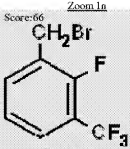


Zoom In

Name: 2-Fluoro-3-(trifluoromethyl)benzyl bromide
IUPAC: 1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene
MF: $C_8H_5BrF_4$
CAS #: 184970-25-0
MW: 257.02
MDL #: MFCD00061172

Score:66

538094 97%

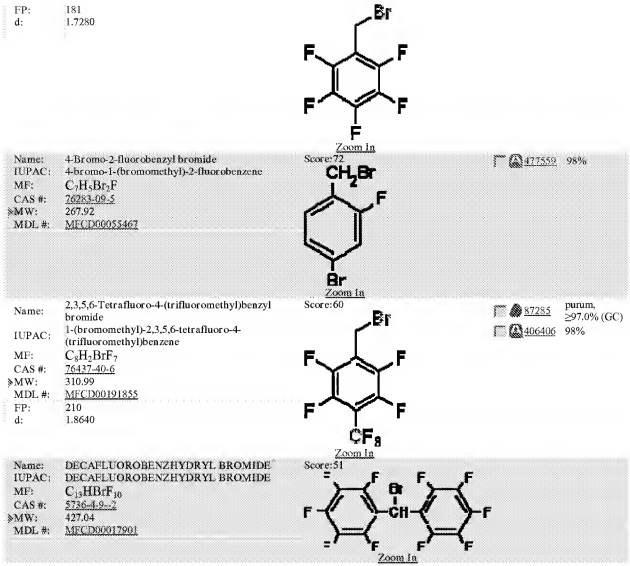


Zoom In

Name: 2,3,4,5,6-Pentafluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene
MF: $C_7H_2BrF_5$
CAS #: 1765-40-8
MW: 260.99
MDL #: MFCD00000299
BP: 174 - 175 °C

Score:81

17910 puriss., ≥99.0% (GC)
101052 99%
33001 ampule of 5 g



Most disturbingly we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made (however the applicant's representative has submitted a screen shot of a catalog that seems to show the commercial availability of these materials). We can see that R_1 can be nothing but fluoro, trifluormethyl or chloro. While many phenols such as 8 are commercial, it would appear that the amide functionality (reverse as well) is required for activity, based on the fact that applicant has no examples of compounds that are not amides (in

the ortho position) and the fact that Xue et. al. (supra) require the amide moiety for antagonism. To the examiners knowledge only one nosylglycidol, namely compound 9, is commercial. Substituents should be limited to lower alkyl.

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required staring materials of formula 1, 2, 8, and 9 are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method

of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). If such starting materials could be obtained compounds could be obtained it is very clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by Grignards (Jie Jack Li *Name Reactions A Collection of Detailed Reaction Mechanisms* "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur (Knochel et. al. *Angew. Chem. Int. Ed.* 2003, *42*, 4302 –4320). The "alkylhalo" compounds will undergo metal halogen exchange when in the presence of a Grignard (Knochel ibid.). The applicant has argued that protecting groups may be used to overcome these limitations, however there are no protecting groups for nitrile or halogen or nitro. How does one protect a halogen, nitrile, or a nitro group?

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the

specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730,734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *Inre Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Another disturbing feature of what is before the examiner, is the fact that it appears that no assays were performed. These compounds may perform in this assay however this has not been asserted. There is no support in the specification for the use of these compounds as chemokine antagonists. While applicant states on pg. 40 "Compounds are evaluated by their

ability to depress the chemotactic response to a standard concentration of M1P-1α chemokine." No evidence is given that these compounds actually were shown to have this activity. Given that similar compounds have the activity we can surmise that the exemplified compounds might have this activity (supra double patenting rejection). The assumption that a chemokine receptor is involved may be incorrect, given that agonism at other GPCRs (δ-opioid receptors for instance), can lead to down regulation of chemokine receptors via heterodimers or higher oligomer complex formation (Chen et. al. *European Journal of Pharmacology* 2004, *483*, 175-186.). The complete receptor profile of THP-1 cells is not known. Applicant may consider a binding assay as in Carroll et. al. WO 00/014086 cited by applicant ref. AG pg. 34:

> The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ^{125}MIP-1α.

or Bondinell et. al. WO 01/64213 A1 pg. 23-25 cited by applicant ref. AH

Biological Data:

CCR5 Receptor Binding Assay

CHO cell membranes (0.25×10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

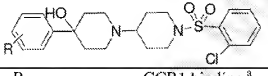
The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 or mCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 µM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists). Alternatively, this CCR5 receptor functional assay was performed on murine CCR5 (mCCR5) with a RANTES concentration of 2nM.

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 µM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators

The applicant regards these compounds as CCR5 antagonists. However MIP-1α is a ligand for both CCR1, CCR3 and CCR5, see Thomson et. al. The Cytokine Handbook 4th Ed. Academic: New York 2003, 1084-1087. It is unclear which receptors these compounds are binding to, or if they are in fact ligands for all three. Regardless, structural requirements for chemokine binding to CCR1, CCR3, and CCR5 are stringent as is well known the art. In the field of CCR1 antagonists many limitations are well known in the art. These compounds are sensitive to structural changes that may be relatively minor in the chemical sense, see Xie, et. al. "Identification of novel series of human CCR1 antagonists," *Bioorganic & Medicinal Chemistry Letters* 2008, 18, 2215–2221.

"Compound 63, where the positions of the halogens were switched, retained comparable potency (63 vs. 61) suggesting the importance of 4-halogen on the phenyl ring. By contrast, replacement of the 4-chloro with the bulky tBu (65) and phenyl (66) groups resulted in total loss of affinity, suggesting a space restriction around this site. All other substituents (for example, OMe, SMe and OPh) led to inactive compounds."

Table 6. SAR of substitution on the left aromatic in the 1, 4'-bipiperidin-4-ol linker series

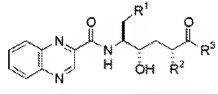


Compound	R	CCR1 binding [a] IC_{50}, μM	Ca^{2+} flux [b] IC_{50}, μM
65	4-tBu	>10	>10
66	4-Ph	>10	>10
67	4-OMe	>10	>10
68	4-SMe	>10	7.98

In fact many substituents are not tolerated at all, resulting in "a total loss of affinity." (C) (E)

As further of evidence of the extreme unpredictability in the CCR1 antagonist development art see Brown et. al. "Novel CCR1 antagonists with improved metabolic stability" *Bioorganic & Medicinal Chemistry Letters* 2004, *14*, 2175–2179:

"Exploration of the C-5 position revealed that a number of halobenzyl C-5 substituents imparted a significant improvement in potency. Most notably, the 3-fluorobenzyl analogue 6j was shown to be >10-fold more potent than the desfluoro analogue 6b and also retained excellent HLM stability. Interestingly, the SAR in this region of the molecule was quite sensitive to minor structural changes. For example, while the 3-fluorobenzyl analogue 6j showed good potency, the closely related 4-fluorobenzyl analogue 6k was inactive."



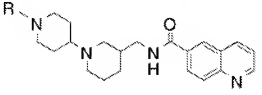
Compound	R^1	R^2	R^3	CCL3 binding IC_{50} (μM)	CCL3 chemo-taxis IC_{50} (μM)
6i	2-Fluorophenyl		NH_2	0.052	0.68
6j	3-Fluorophenyl		NH_2	0.046	0.065
6k	4-Fluorophenyl		NH_2	>25	>25

Here it is very clearly shown that what appears to a relatively innocuous change results in compounds with no activity. (C) (E)

CCR3 activity is also highly dependent upon the structure of the compound in particular N-Benzyl piperdines are well-known to have limitations on the substituents on the phenyl ring, see Ting et. al. "The synthesis of substituted bipiperidine amide compounds as CCR3 ligands: Antagonists versus agonists" *Bioorganic & Medicinal Chemistry Letters* 2005 15, 3020–3023:

"The monosubstituted 2-chloro analogue 11c is inactive while the 4-chloro analogue 11d shows reasonable CCR3 affinity. The saturated cyclohexylmethyl analogue 11e is completely inactive. Methyl substitution at the benzylic position as in 11f or extension to the 3,4-dichlorophenethyl as in 11g also decrease affinity. Replacement of the 3,4-dichlorobenzyl moiety with the corresponding vamide moieties as in compounds 11h and 11i or the urea moiety as in compound 11j also produces inactive analogues."

Table 2. In vitro CCR3 membrane binding and agonist (GTPγS) activity of benzyl bipiperidine analogues **4i** and **11a–j**



Compd	R	K_i (nM)	E_{max}% GTPγS[a]
4i	3,4-DiCl-PhCH$_2$	23 ± 1	−7
11a	3,5-DiCl-PhCH$_2$	398 ± 59	45
11b	2,5-DiCl-PhCH$_2$	391 ± 44	45
11c	2-Cl-PhCH$_2$	36%[a]	NT
11d	4-Cl-PhCH$_2$	95 ± 7	−8
11e	CyclohexylCH$_2$	17%[b]	NT
11f	3,4-DiCl-PhCHMe	74 ± 3	−12
11g	3,4-DiCl-PhCH$_2$CH$_2$	180 ± 32	2
11h	3,4-DiCl-PhCO	20%[b]	NT
11i	3,4-DiCl-PhCH$_2$CO	767 ± 16	NT
11j	3,4-DiCl-PhNHCONH	6%[b]	NT

NT = not tested.
[a] E_{max}% at 10 μM (n = 2).
[b] % inhibition at 1 μM (n = 2).

It is quite notable that all the compounds of the instant case have a dichlorophenyl moiety in the position corresponding to the R of Table 2 of Ting.

For CCR5 ligands many limitations are well known in the art. In a study of similar compounds Thoma, et. al. "Orally Bioavailable Competitive CCR5 Antagonists" *Journal of Medicinal Chemistry* 2004, *47*, 1939-1955, made the following statement, about substituents on the phenyl rings:

"First we explored a few analogues of the highly potent
CCR5 antagonist 1a with a cyano substituent in different
positions of the benzyl group (Table 1). The 3-substituted
compound 1c was found to be even more potent
than unsubstituted 1a on both human and cyno CCR5.
The 2-substituted derivative 1b was significantly less
potent than 1a in the human binding assay but highly
inferior in the Ca2+-mobilization assay. In addition, it
was found to be almost inactive on cyno CCR5. The
4-substituted derivative 1d was considerably less potent
than 1c. Compound 1e with a trimethoxybenzyl group
was found to be completely inactive. These findings
suggest that substituents of the benzyl group are well tolerated
in the 3-position but can significantly reduce
the affinity when attached to other ring positions.
Furthermore, the substitution pattern seems to affect
the reactivity on human vs cyno CCR5." Pg. 1941 (C & E)

Thus it is clear that substitution can have a very pronounced impact on the active pharmacophore, and a choice of the wrong substituent or too many substituents gives compounds with no activity. The claims here may have many substituents most of which are prophetic. All the working examples have very limited substituents.

We have been given no information in regard to the molecular determinants of chemokine inhibition for the compounds of the instant case. (F & G) The factors outlined in *In Re Wands* mentioned above apply here, and in particular as per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled

in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only two working examples in this unpredictable art without undue experimentation. (C, E, F, G, H).

Conclusion

10. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
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